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Addition of Organometallic Reagents to Chiral *N*-Methoxylactams: Enantioselective Syntheses of Pyrrolidines and Piperidines

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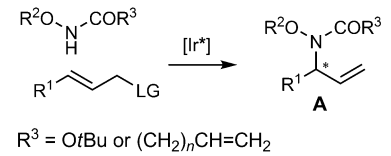
Abstract: Enantioselective iridium-catalyzed allylic substitutions were used to prepare *N*-allyl hydroxamic acid derivatives that were suitable for ring-closing metathesis, giving *N*-methoxylactams. Reactions of these derivatives with Grignard or organolithium compounds gave hemiaminals, which could be reduced diastereoselectively via acyliminium intermediates to give *cis*-piperidines or *cis*-pyrrolidines with substituents in the 2,6- or 2,5-positions, respectively. In addition, compounds with a quaternary carbon center could be synthesized by corresponding reactions with potassium cyanide/AcOH. The procedures were applied in the syntheses of alkaloids (−)-209D and (+)-prosophylline.

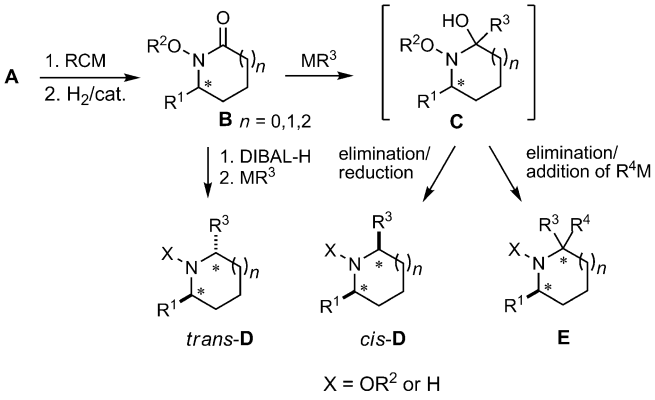
Keywords: alkaloids · allylic compounds · enantioselectivity · iridium · lactams

Introduction

We have recently developed an asymmetric Ir-catalyzed allylic amination procedure by using *N*-alkoxy amides as nucleophiles that allows chiral *N*-allylated hydroxylamines **A** to be prepared efficiently with high enantiomeric purity and broad scope with respect to substituents R^1–R^3 (Scheme 1).[1] Being interested in applications of allylic amines in the synthesis of pyrrolidine and piperidine alkaloids,[2] we have also successfully probed a nucleophile containing an olefinic moiety, $R^3 = CH_2CH{=}CH_2$, yielding a product suitable for ring-closing metathesis (RCM) to give a piperidine derivative **B** (Scheme 2). Subsequently, we have extended this approach and are now able to report enantio- and diastereoselective syntheses of a variety of five- and six-membered cyclic hydroxamic acid derivatives of type **B** with enantiomeric excess of more than 90%.



Scheme 1. Ir-catalyzed allylic substitution with hydroxamic acid derivatives.



Scheme 2. Preparation of α,α′-disubstituted pyrrolidines and piperidines from allylic amines.

Furthermore, as most of the aforementioned alkaloids contain substituents at both α-positions of the azacycle, we have investigated reactions of compounds **B** with organolithium and Grignard compounds that would open a route to hemiaminals of type **C** and subsequently iminium salts and/or enamines with their vast synthetic potential (Scheme 2). It should be noted that targets **D** can be generated with *cis*- as well as *trans*-configuration by first reduction and then addition of a metal organyl, respectively.

At the outset we could build on experience with Weinreb amides RCON(OMe)Me[3] and the pioneering work of the Kibayashi group[4] on alkaloid syntheses with bicyclic *N*-acyl-hydroxylamines prepared by intramolecular cycloaddition of nitroso compounds. While our work was in progress, Kouklovsky, Vincent et al. published further work with bicyclic *N*-alkoxylactams, generated by a cycloaddition approach with nitroso compounds that differed from those used by the Kibayashi group.[5] Finally, Chida, Sato et al. reported

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bottom-up studies that recently also included achiral and a few racemic monocyclic *N*-alkoxy-lactams.[6] These authors have very recently studied route **B** → *trans*-**D**, which we have not pursued.[6a] The steric course of the addition reactions depicted in Scheme 2 is in accordance with general rules concerning additions to iminium ions,[6a, 7] that is, preferred axial attack of the nucleophile at the iminum ion in the half-chair conformation.

The approach sketched out above is not without problems. Thus, lability of the N–O bond makes it vulnerable to reductive cleavage,[8] which would limit reactions with reagents of the type MR^4 (R^4 = H). Reducing agents, however, are quite selective. For example, the N–O bond is cleaved upon catalytic hydrogenation with Raney nickel as catalyst whereas it is unaffected with Pd/C. Experience with Weinreb amides has revealed that elimination reactions giving either imines or formaldehyde, are fairly common.[9]

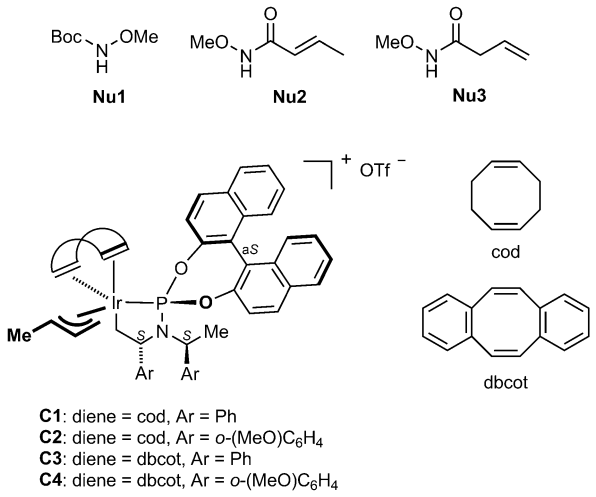
We want to point out that our objective can, in principle, also be reached by direct addition of metal organyls to amides followed by reduction. The limits of this approach are, however, well-known. Nevertheless, some examples for the diastereoselective addition of Grignard reagents to bicyclic amides followed by reduction have been reported.[10] Reductive alkylations of monocyclic lactams are even less common.[11] In general, amides require preactivation prior to nucleophilic addition.[12] General used strategies are transformation into the corresponding thioamides,[13,14] lactim ethers,[15] or iminium triflates.[16] The latter method was recently extended to include pyrrolidines and piperidines and applied in alkaloid synthesis.[16d]

A widely adopted method is the conversion of *N*-acyl derivatives into *N*-acyliminium ions, which readily react with various types of nucleophiles.[17] In this case, the route to α,α′-disubstituted pyrrolidines or piperidines almost exclusively involves first reduction, then addition of acid to generate the acyliminium ion, which is then alkylated. The reverse sequence, in analogy to Scheme 2, is uncommon, likely because of ring opening at the hemiaminal stage.[18]

Results and Discussion

Ir-catalyzed allylic amination: The Ir-catalyzed allylic substitution is a reliable method for the synthesis of branched allylic compounds with a high degree of regio- and enantioselectivity.[19] Monosubstituted carbonates are normally used as substrates. Recently, stable (π-allyl)Ir-complexes have become readily accessible and, therefore, can be used as single-species catalysts.[20] As pointed out above, hydroxamic acid derivatives are suitable N-nucleophiles that give *N*-allylated hydroxylamines. In the present work, the three pronucleophiles **Nu1**–**Nu3** were employed in conjunction with "salt-free"[21] reaction conditions (Figure 1).

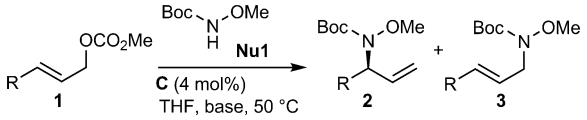
Allylic substitution with **Nu1** constitutes the most general access to the requisite allylic hydroxylamines (Table 1). Substitution reactions were remarkably fast with all the allylic substrates of type **1** probed. Regio- and enantioselectivity



C1: diene = cod, Ar = Ph
C2: diene = cod, Ar = *o*-(MeO)C_6H_4
C3: diene = dbcot, Ar = Ph
C4: diene = dbcot, Ar = *o*-(MeO)C_6H_4

Figure 1. Pronucleophiles, (π-allyl)Ir complexes and achiral ancillary ligands used.

Table 1. Ir-catalyzed allylic substitution with pronucleophile **Nu1**.



1a-e, **2,3a,c,d** **a** R = Ph, **b** R = nC_4H_9, **c** R = nC_6H_{13}, **d** R = CH_2OBn, **e** R = CH_2OPMB

	Substrate	Catalyst	Base	*t* [h]	Yield [%][a]	**2**/**3**[b]	*ee* [%][c]
1	**1a**	**C2**	TBD	1.5	59	96:4	98
2	**1c**	**C4**	DBU	2	90	98:2	94
3	**1d**	**C4**	DBU	1	71	90:10	88
4	**1d**	**C3**	DBU	3	77	93:7	93

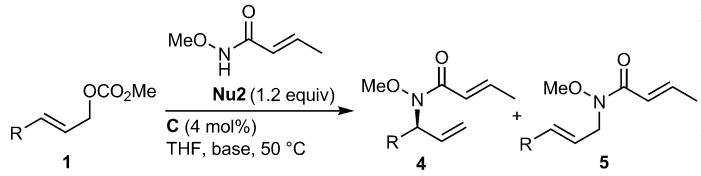
[a] Combined yield of **2**+**3**. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude product. [c] Determined by HPLC analysis.

were particularly high for the reaction of substrate **1a** catalyzed by **C2** (Table 1, entry 1). Complex **C4**, with dbcot (dbcot = dibenzocyclooctatetraene) as an ancillary ligand, was used for substrates **1c** and **d** (Table 1, entries 2 and 3). For **1d**, further improvement was possible by using **C3**, derived from ligand **L1**, as catalyst (Table 1, entry 4).

Following our general concept, the use of pronucleophile **Nu2** was probed (Table 2). This compound was readily prepared from ethyl crotonate and *O*-methylhydroxylamine hydrochloride by using a procedure developed by Gissot et al.[22] The Ir-catalyzed allylic amination of carbonate **1a** with **Nu2** proceeded smoothly to give **4a** with excellent regio- and enantioselectivity.

Next, reactions with the more demanding pronucleophile **Nu3** were investigated (Scheme 3). This pronucleophile, as well as the substitution products **6**, can rearrange under basic reaction conditions to the corresponding crotonamides **Nu2** and **4**, respectively. Indeed, reaction of the allylic carbonates gave mixtures of the branched products **6** and **4** with modest enantioselectivity. Therefore, we decided to

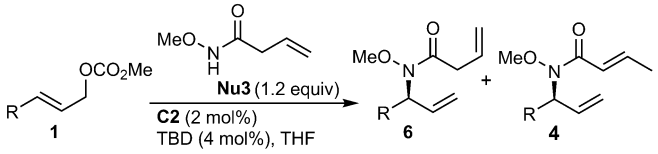
Table 2. Ir-catalyzed allylic substitution with the pronucleophile **Nu2**.



1,**4**,**5** **a** R = Ph, **b** R = nC_4H_9, **e** R = CH_2OPMB

	Substrate	Catalyst	Base	*t* [h]	Yield [%][a]	**4**/**5**[b]	*ee* [%][c]
1	**1a**	**C2**	TBD	1	92	97:3	96
2	**1b**	**C2**	DBU	17	76	93:7	96
3	**1b**	*ent*-**C1**[d]	DBU	17	80	92:8	95
4	**1e**	*ent*-**C1**[d]	DBU	7	64	80:20	92

[a] Isolated yield of branched isomer. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude product. [c] Determined by HPLC analysis. [d] 8 mol% catalyst was used.



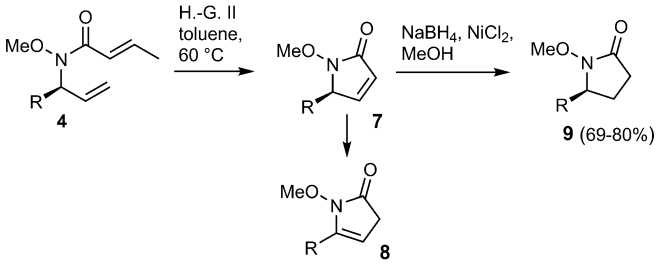
1,**4**,**6** **c** R = nC_6H_{13}, **d** R = CH_2OBn

6c, 39%, 89% *ee* + **4c**, 16%
6d, 46%, 77% *ee* + **4d**, 18%

Scheme 3. Ir-catalyzed amination with **Nu3**.

carry out the Ir-catalyzed amination with the Boc-protected pronucleophile **Nu1** and to install the enoyl group afterwards.

Cyclic hydroxamic acid derivatives: Pyrrolidinones **9** (Scheme 4) were prepared in good yields from substitution products **4** by ring-closing metathesis (RCM) in toluene as solvent and subsequent reduction with sodium borohydride/nickel chloride.[23] This seemingly simple route required a considerable amount of optimization because of a marked tendency of the primarily formed conjugated *N*-methoxylactam **7** to rearrange to enamine **8**.[24] This rearrangement occurred upon contact with silica or alumina. Chromatographic purification of **7** turned out to be possible with solvents containing acetic acid; however, it was advantageous to

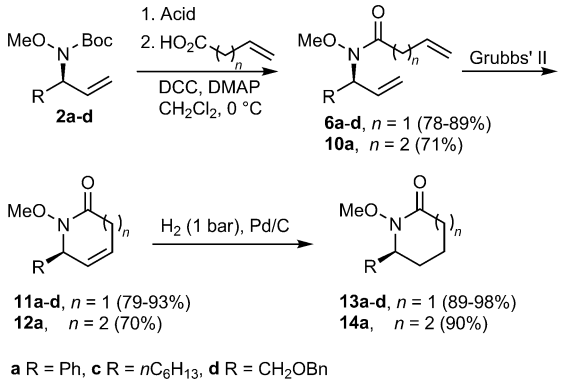


4,**7**-**9** **a** R = Ph, **b** R = nC_4H_9, **e** R = CH_2OPMB

Scheme 4. Synthesis of *N*-methoxypyrrolidones.

reduce crude **7** directly. The enantiomeric excess of **9a** was found to be identical to that of the starting material **4a**.

Hexa- and heptacyclic hydroxamic acid derivatives were obtained from the branched allylic substitution products **2** as depicted in Scheme 5. Boc deprotection with trifluoroacetic acid (TFA) or hydrochloric acid followed by Steglich acylation[25] with vinylacetic acid or allylacetic acid gave dienes **6** and **10**, respectively, which were subjected to RCM to give olefins **11** and **12**, respectively. Hydrogenation of the double bond without cleavage of the N–O bond was carried out with Pd/C as catalyst and gave the hydroxamic acid derivatives **13** and **14** in good overall yields.



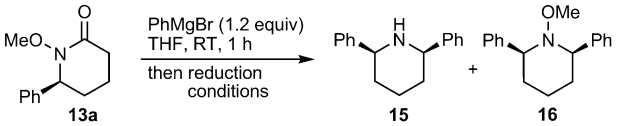
a R = Ph, **c** R = nC_6H_{13}, **d** R = CH_2OBn

Scheme 5. Synthesis of hexa- and heptacyclic hydroxamic acid derivatives.

Alkylation/reduction of hydroxamic acid derivatives; Optimization of reaction conditions and mechanistic aspects: *N*-Methoxylactam **13a** was chosen as test substrate for identification of suitable conditions for the nucleophilic addition and subsequent reduction to 2,6-disubstituted piperidines (cf. Scheme 2). The reaction of phenylmagnesium bromide with **13a** in tetrahydrofuran (THF) proceeded smoothly at room temperature with full conversion after one hour. Work-up by addition of water, extraction with ethyl acetate, and concentration of the extract in vacuo gave the crude product, which was analyzed by ^{1}H and ^{13}C NMR spectroscopy. The spectra were consistent with a mixture of diastereomers of the expected N,O-hemiaminal (cf. **C**; R^1, R^3 = Ph, R^2 = OMe, Scheme 2).

The crude material was subjected to catalytic hydrogenation (1 bar) with transition-metal catalysts to yield known 2,6-diphenylpiperidine (**15**)[26] (Table 3). Under all conditions tried, only *cis*-**15** was formed, the *trans*-diastereomer was not detected by ^{1}H or ^{13}C NMR spectroscopic analysis. With palladium on charcoal and Pearlman's catalyst, the reaction times were long and the isolated yields low, the N–O bond was cleaved during hydrogenation (Table 3, entries 1 and 3). Acidification with acetic acid led to acceleration of the reduction, and product **15** was isolated in an improved yield of 55% (Table 3, entry 2). The use of platinum on charcoal and platinum derived from PtO_2 led to mixtures of

Table 3. Alkylation/reduction starting from **13a**.



13a 15 16

	Reduction conditions	Procedure[a]	t [h]	**15**/**16**[b]	Yield [%][c]
1	H_2, Pd/C, EtOH	A	42	>99:1	28
2	H_2, Pd/C, MeOH/AcOH (9:1)	A	5	92:8	55
3	H_2, $Pd(OH)_2$/C, MeOH	A	48	96:4	17
4	H_2, Rh/C, MeOH	A	48	100:0	38
5	H_2, Pt/C, MeOH	A	48	75:25	n.d.
6	H_2, PtO_2, MeOH	A	48	37:63	n.d.
7	H_2, Raney nickel, MeOH	A	18	>99:1	88
8	$NaBH_3CN$, AcOH	B	1.5	<1:99	87
9	$NaBH_4$, AcOH	B	1.5	<1:99	80
10	$NaB(OAc)_3H$, AcOH	B	2	<1:99	86
11	$NaBH_3CN$, $Sc(OTf)_3$ (20 mol%), THF	B	2	<1:99	80

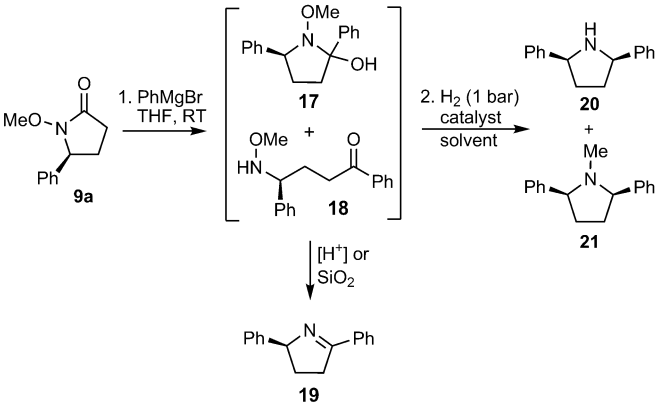
[a] Procedure A: A suspension of crude hemiaminal and catalyst (20 wt%) in the stated solvent was stirred under hydrogen atmosphere (1 bar) at RT; Procedure B: After the reaction with the Grignard reagent, AcOH (excess) and then the complex metal hydride (5 equiv) were added. [b] Determined by GC-MS analysis or ^{1}H NMR spectroscopic analysis of the crude product. [c] Isolated yield, only one diastereomer found.

the piperidine and *N*-methoxypiperidine (Table 3, entries 5 and 6). Finally, Raney nickel turned out to be the catalyst of choice. Thus, *cis*-2,6-diphenylpiperidine (**15**) was obtained as a single product in 88% yield over two steps (Table 3, entry 7).

Clear drawbacks of catalytic hydrogenation are restriction to substrates with saturated side chains and cleavage of the N–O bond. Therefore, application of acid-stable complex hydrides, $NaBH_3CN$,[27] $NaBH_4$/AcOH,[28] and $NaB(OAc)_3H$/AcOH were examined as reducing agents. The reactions were carried out as follows. A solution of *N*-methoxylactam **13a** in THF was treated with the organometallic reagent; after complete consumption of the starting material, an excess of acetic acid and then the reducing agent were added. The three reductants gave similar results (Table 3, entries 8–10). An additional experiment with $Sc(OTf)_3$ instead of acetic acid required aqueous work-up after the addition of the Grignard reagent but also gave acceptable results (Table 3, entry 11). All these reductions proceeded in good yields and with perfect *cis*-diastereoselectivity according to ^{1}H and ^{13}C NMR spectroscopic analysis. The *N*-alkoxy group can either be utilized as a protecting group in further transformations, or easily cleaved with Zn/AcOH or SmI_2.[8]

The optimal conditions were then applied to butyrolactam **9a** (Scheme 6). NMR spectroscopic analysis of the crude product obtained after addition of PhMgBr and aqueous work-up revealed a mixture of the N,O-hemiaminal **17** and acyclic ketone **18**, which were both unstable, but were characterized by ^{1}H and ^{13}C NMR spectroscopic analysis. After a few hours storage, a further compound was detected that turned out to be imine **19**.[29] The formation of **19** could be accelerated by addition of an acid or silica gel, to the extent that is was obtained as the main product. Accordingly, the crude product from the addition of the Grignard reagent had to be immediately reduced. Reduction with H_2/$Pd(OH)_2$/C (Pearlman catalyst) in ethanol furnished a mixture of pyrrolidine **20** and the *N*-methyl derivative **21** (Table 4, entry 1). With Raney nickel as catalyst, *N*-methylation also occurred in the solvents methanol and isopropanol (Table 4, entries 2–4), which indicates that the *N*-methyl group was derived from the N-OCH_3 moiety. N-Methylation was almost completely avoided with a THF/water mixture as solvent (Table 4, entry 5); under these conditions, *cis*-2,5-diphenylpyrrolidine (**20**) was isolated in 76% yield and the *trans* isomer was not detected. Compounds **20**[30] and **21**[30] have been reported in the literature and were characterized by ^{1}H and ^{13}C NMR spectroscopy.

To verify that the *N*-methyl group originated from the O-methyl group and to gain insight into the mechanism of formation of **21**, control experiments with the O-CD_3 analogue of **9a** were carried out under the developed conditions (Table 4, entries 4 and 5; Scheme 7). These reaction conditions



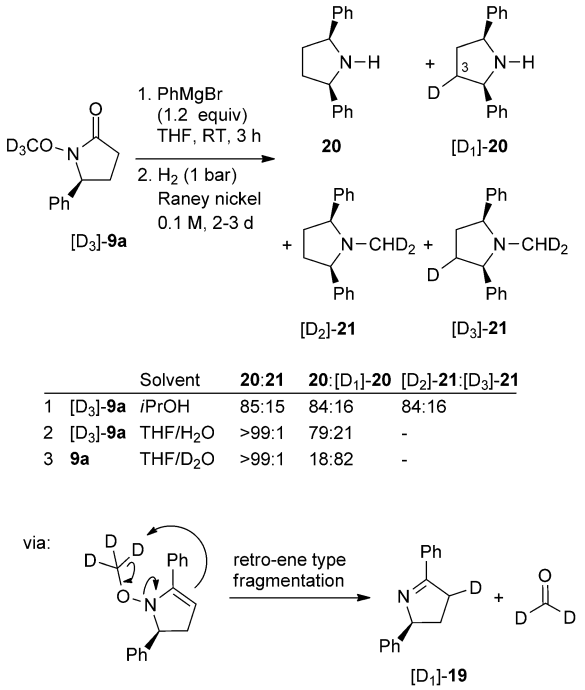
Scheme 6. Alkylation/reduction of *N*-methoxylactam **9a**.

Table 4. Alkylation/catalytic hydrogenation of **9a** according to Scheme 6.

	Catalyst	Solvent	t [h]	**20**/**21**[a]	Yield of **20** [%][b]
1	$Pd(OH)_2$/C	EtOH	20	33:67	n.d.
2	Raney nickel	MeOH	48	66:34	n.d.
3	Raney nickel	EtOH	120	73:27	n.d.
4	Raney nickel	*i*PrOH	96	73:27	n.d.
5	Raney nickel	THF/H_2O	72	98:2	76

[a] Determined by GC-MS analysis of the crude products. [b] Isolated yield.

indeed furnished the *N*-CHD_2-amine [D_2]-**21** as expected for a pathway involving elimination of water to give an enamine, elimination of formaldehyde, imine reduction, and reductive amination. In addition to [D_2]-**21**, compound [D_3]-**21** was detected by HRMS analysis of the hydrogenation products; according to the NMR assignment, this species contained an N-CHD_2 group and one D at C-3 of the pyrrolidine moiety, albeit only to the extent of 15–20%. Control



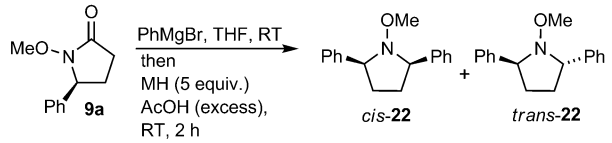
Scheme 7. Alkylation/hydrogenation of deuterium labeled [D_3]-**9a**.

experiments (Scheme 7, entries 2 and 3) with THF/H_2O and THF/D_2O as solvents revealed that H/D exchange at C-3 occurs to a considerable degree during the reaction sequence.

The above observations are compatible with, at least in part, an intramolecular retro-ene type fragmentation transferring one D to C-3 and yielding D_2C=O (cf. Scheme 7). As pointed out above, fragmentation reactions under strongly basic as well as acidic conditions are well-known.[9] A cyclic retro-ene reaction of this type has been proposed but not verified so far.[9a,31]

Alkylation of butyrolactam **9a** followed by reduction with complex metal hydrides in acetic acid was straightforward (Table 5). *N*-Methoxypyrrolidine **22** was formed in good yield, however, with varying degrees of diastereoselectivity in favor of the *cis*-isomer. For an unambiguous configurational assignment, *trans*-**22** was prepared by reduction of **9a** with diisobutylaluminum hydride (DIBAL-H) and subsequent addition of phenylmagnesium bromide, by using a procedure developed by the Chida group[6a] (see the Supporting Information). In addition, *cis*- and *trans*-**22** were reduced to pyrrolidines **20**. Whereas the diastereoselectivity was modest with $NaBH_4$ or $NaB(OAc)_3H$ (Table 5, entries 1 and 2), it was excellent with $NaBH_3CN$, especially when acetic acid was replaced by a Lewis acid (Table 5, entries 3 and 4). However, in the latter case, the yield of **22** was low and imine **19** was formed as by-product.

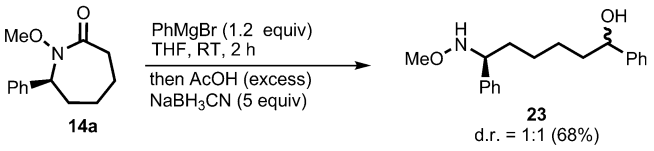
Table 5. Alkylation/complex hydride reduction of **9a**.



	Reducing agent	d.r.[a]	Yield of **22** [%][b]
1	$NaBH_4$	5:1	77
2	$NaB(OAc)_3H$	6:1	80
3	$NaBH_3CN$	15:1	85
4	$NaBH_3CN$, $Sc(OTf)_3$ (20 mol%)	>20:1	42

[a] Determined by GC-MS analysis of the crude products. [b] Isolated yield.

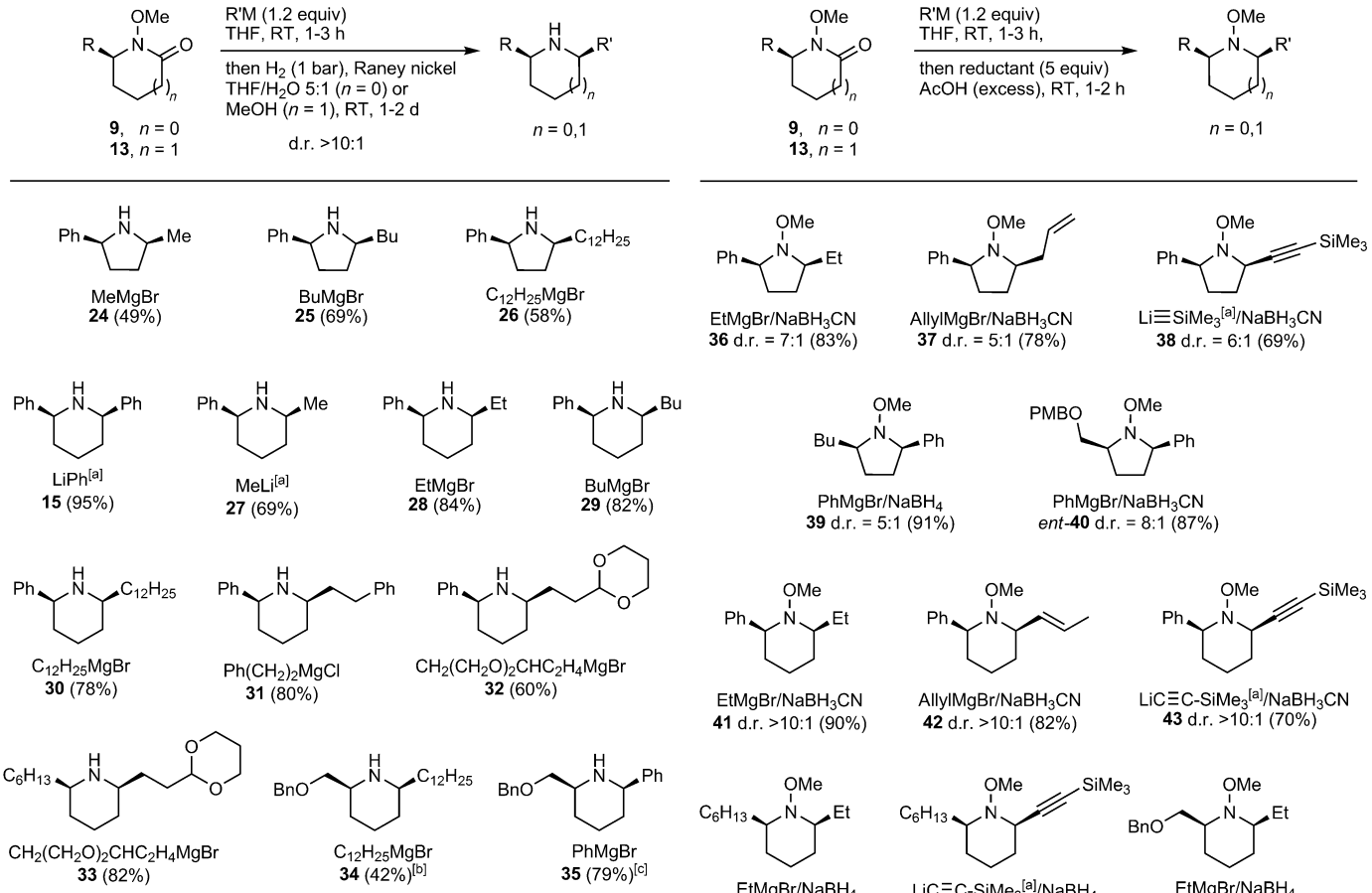
Experiments with the seven-membered ring analogue revealed some limits of the procedure, with ring-opened products being obtained almost exclusively (Scheme 8). Thus, reaction of **14a** with phenylmagnesium bromide followed by hydrogenation over Raney nickel in methanol gave a mixture of products, from which the expected 2,7-diphenylazepane was isolated in less than 5% yield (not shown). Reduction with $NaBH_3CN$/AcOH (cf. Scheme 8) gave acyclic alcohol **23** as mixture of diastereomers in 68% yield. Clearly, opening of the hemiacetal intermediate is the dominating reaction in this case.



Scheme 8. Alkylation/metal hydride reduction of **14a**.

Scope of the alkylation/reduction procedure to give α,α′-disubstituted pyrrolidines and piperidines: The scope of the addition/reduction sequence was then probed. Addition of Grignard reagents to the five-membered *N*-methoxy-lactam **9a**, and subsequent catalytic hydrogenation with Raney nickel under the optimized conditions, furnished *cis*-2,5-di<-substituted pyrrolidines in moderate to good yields and with high diastereoselectivity (Scheme 9, products **24**–**26**); the ^{13}C NMR spectra of all products displayed only one set of signals. The relative *cis* configuration of **24** was established by comparison with the reported NMR data for *cis*- as well as *trans*-**24**.[32] By analogy, assumption of the *cis*-configuration for **25** and **26** appears warranted.

The reactions of the six-membered *N*-methoxy-lactams likewise gave *cis*-2,6-disubstituted piperidines in good to excellent yield with high diastereoselectivity (Scheme 9, products **15** and **27**–**35**). Alkyl, aryl as well as functionalized alkyl groups were probed as substituents. The 1,3-dioxan-2-yl ethyl group allows preparation of bicyclic compounds through subsequent reductive amination, as will be described later. In the addition step, organolithium reagents react at −78°C, whereas Grignard reagents require room temperature. In all cases, *cis* isomers were obtained with excellent diastereoselectivity (more than 10:1). The configurational assignment was based on comparison with literature



Scheme 9. Alkylation/catalytic hydrogenation of *N*-methoxylactams. In the product formulas, the substituent R is presented at the left. Diastereomeric ratios were determined by GC-MS analysis or on the basis of ^{1}H NMR spectroscopic analysis of the crude products. See the Supporting Information for a more detailed table. [a] The reaction was carried out at −78 °C. [b] In addition, 35 % of benzyl-deprotected product was isolated. [c] A mixture of Raney nickel and Pd/C was used as catalyst.

Scheme 10. Alkylation/complex metal hydride reduction of *N*-methoxylactams. In the product formulas, the substituent R is presented at the left. See the Supporting Information for a more detailed table. Diastereomeric ratio was determined by GC-MS analysis or on the basis of ^{1}H NMR spectroscopic analysis of the crude products. [a] The reaction was carried out at −78 °C.

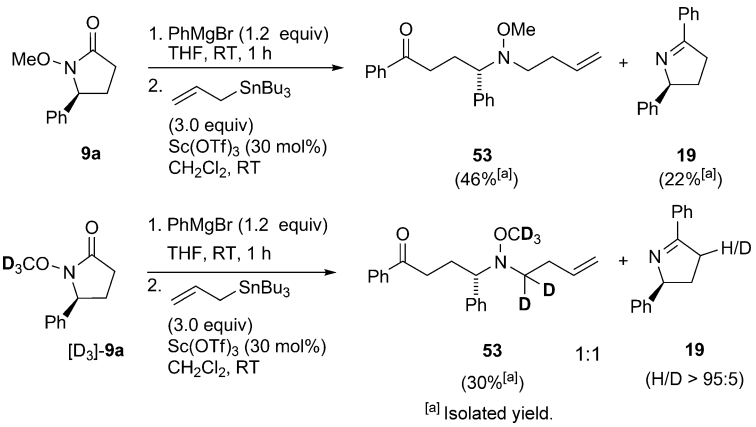
data (**15**,[26] **27**,[33] **29**,[33a] and **31**[34]); the axial disposition of both 2-H and 6-H was apparent from vicinal coupling constants (J = 10.4–10.8 and 2.2–2.5 Hz) for all products. For a few selected examples the *cis*-configuration was further verified by NOESY experiments (see the Supporting Information).

The scope of the alkylation/metal hydride reduction sequence is summarized in Scheme 10. With *N*-methoxybutyrolactams, moderate to good diastereoselectivities in favor of the *cis*-products were obtained (Scheme 10, **36**–**40**). The introduction of unsaturated side chains, for example allyl- (**37**) and 2-trimethylsilylethinyl (**38**) groups, was possible with this sequence. As reducing agents, $NaBH_3CN$, $NaBH_4$, $NaB(OAc)_3H$ and DIBAL-H were investigated (see the Supporting Information for a detailed table). Diastereoselectivities (5:1 to 8:1) of reductions with compounds derived from phenyl-substituted **9a** were optimal with $NaBH_3CN$/AcOH, whereas $NaBH_4$/AcOH gave significantly superior yield and diastereoselectivity in the case of butyl-substituted products derived from **9b**. The stereochemical assignments were made as follows. For **39**, the diastereoisomers were separated and individually characterized by NMR spectroscopic analysis, including NOESY experiments. Furthermore, as an empirical correlation, it was found that coupling constants of the protons NC*H*(Ph) were 9–10 Hz for the major *cis*-isomers and 7.0–7.6 Hz for the minor *trans*-isomers.

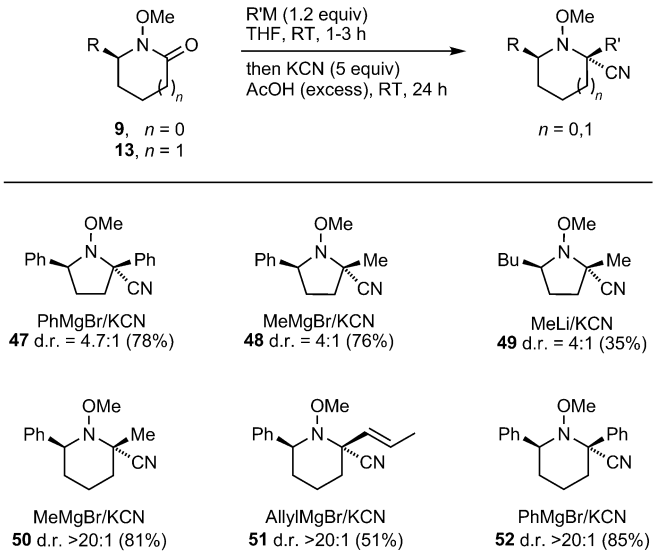
The six-membered *N*-methoxy-lactams gave *cis*-2,6-disubstituted piperidines in high yield (Scheme 10, **41**–**46**). Reductions of hemiaminals derived from phenyl-substituted lactam **13a** were best carried out with $NaBH_3CN$/AcOH, whereas $NaBH_4$ was better suited for hemiaminals derived from the alkyl-substituted starting materials **13c** and **13d**. The addition of allylmagnesium bromide to **13a** gave a hemiaminal with a prop-1-enyl group (NMR analysis), and subsequent reduction produced **42** with an internal double bond. The corresponding isomerization did not occur in the case of the five-membered *N*-methoxy-lactam (Scheme 10, **37**).

Configurations of the major *cis*-products were assigned on the basis of the ^{1}H NMR coupling constants of the axial 2-H and 6-H ($J = 10.4$–11.9 Hz and 2.3–3.1 Hz). In the case of **44** and **45**, ^{1}H and ^{13}C NMR spectral assignment was possible for the *cis*- as well as the *trans*- diastereomer.

Trisubstituted pyrrolidines and piperidines: Build-up of quaternary centers is of continuing interest in organic synthesis. Chida et al.[6a] have explored reactions of *N*-benzyloxylactams with organolithium reagents and subsequent addition of trimethylsilyl cyanide (3 equiv) and $SnCl_4$ (1.3 equiv). Although the use of various six-membered lactams gave rise to pure diastereomers, only one example of a five-membered lactam was investigated, which displayed low diastereoselectivity of 1.3:1. Application of this procedure to **9a** mainly furnished imines, that is, elimination products. Similarly, the addition of a Grignard reagent to **9a** followed by Lewis acid promoted allylation (Scheme 11) gave rise to imine **19** and the ring-opened allylation product **53**, although the yield and reproducibility of these reactions were low. According to a control experiment with [D_3]-**9a**, [D_5]-**53** is formed by elimination to give formaldehyde, imine formation and addition of the allyltin reagent. Clearly, *N*-methoxylactams are less stable to Lewis acids than *N*-benzyloxylactams.



Scheme 11. Attempted addition of Grignard reagent followed by allylation.



Scheme 12. Alkylation/cyanide addition of *N*-methoxylactams. A more detailed table is included in the Supporting Information. Diastereomer ratios were determined by ^{1}H NMR spectroscopic analysis of the crude products.

Fortunately, we found that the simple procedure described above for reductions with complex hydrides was also suitable for addition of cyanide (Scheme 12). Thus, reaction of the *N*-methoxylactam with a Grignard reagent followed by addition of KCN and acetic acid furnished amino nitriles **47**–**52** in good to high yield. Diastereoselectivity was very high (more than 20:1) for the six-membered ring and moderate (ca. 4:1) for the five-membered ring compounds. For the preparation of **49**, methyl magnesium bromide was not suitable, whereas methyl lithium furnished a yield of 35% and diastereomeric ratio of 4:1. The configuration of **47** was determined by an X-ray crystal structure analysis (see the Supporting Information). The configurations of **48** and **50** were corroborated by the close resemblance of their NMR data to those of the analogous *N*-benzyloxylactams. Clearly, the steric course of the reduction and cyanation are very similar, that is, axial approach of the nucleophile to the iminium ion.[6a]

Syntheses of alkaloids (−)-209D and (+)-prosophylline: Piperidines and pyrrolidines are structural motifs of numerous biologically active compounds, in particular alkaloids,[35] and are often used as probes for new synthetic procedures. Widely occurring among alkaloids are *cis*-2,6-disubstituted piperidines, in particular compounds with an additional 3-OH group, and *cis*-2,5-disubstituted pyrrolidines. More complex bicyclic structures, for example indolizidines, are often derived from the monocyclic heterocycles by an additional reductive amination step (Figure 2). Many methods for the stereoselective synthesis of all these alkaloids have been developed.[36,37] However, the number of methods based on asymmetric catalysis is still quite small.[38] To broaden the repertoire of such syntheses and to test the applicability of the procedures described above, we synthesized indolizidine (−)-209D and 3-hydroxypiperidine alkaloid (+)-prosophylline. So far only one *enantioselective* synthesis of (+)-prosophylline has been reported.[39]

The synthesis of the indolizidine alkaloid (−)-209D is detailed in Scheme 13. Reaction of (1,3-dioxan-2-ylethyl)-magnesium bromide with **13c**, prepared from **2c** (94% *ee*), and subsequent catalytic hydrogenation with Raney nickel as

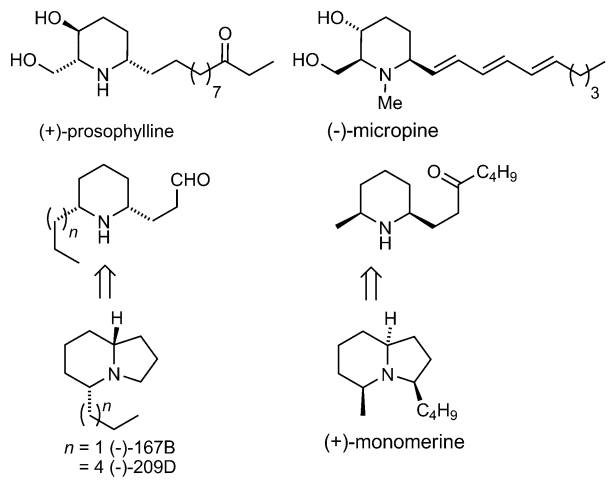
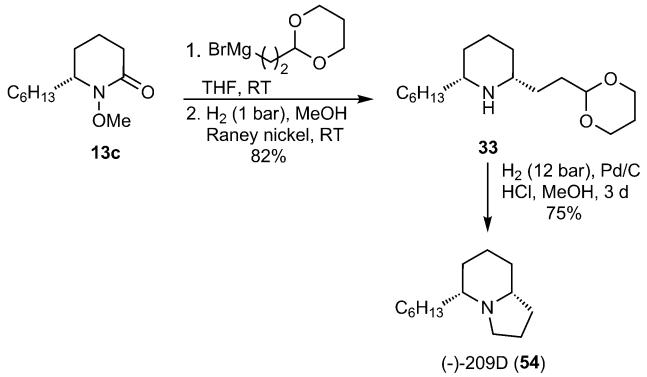
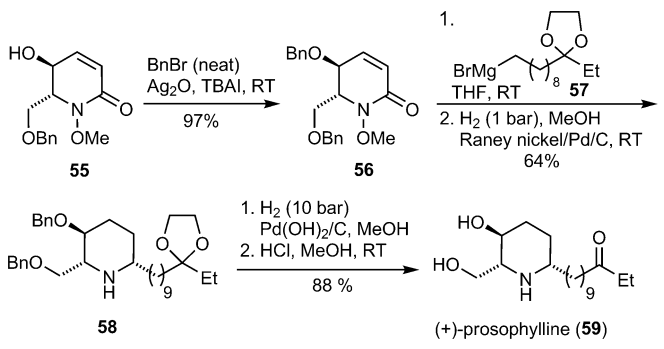


Figure 2. Examples of 2,6-disubstituted piperidine alkaloids.



Scheme 13. Synthesis of indolizidine (−)-209D.

catalyst, furnished **33** in 82% yield over two steps. Deprotection of the aldehyde and reductive amination were carried out in one pot by using palladium on charcoal in acidified methanol. Elevated hydrogen pressure and long reaction times were required to obtain full conversion. The reductive amination proceeded with perfect *cis*-diastereoselectivity to give alkaloid (−)-209D in 75% yield; the spectral data matched the reported data {$[\alpha]_D^{20} = -60.6$ ($c = 1.14$, $CHCl_3$); lit.:[40e] $[\alpha]_D^{20} = -66.5$ ($c = 1.00$, $CHCl_3$)}.[10b, 40]



Scheme 14. Synthesis of (+)-prosophylline.

Starting material for the synthesis of (+)-prosophylline was *N*-methoxylactam **55** (Scheme 14), which was obtained from **2d** (93% *ee*) in 48% yield in four steps using a route reported by us.[1a] Standard protection gave O-benzyl derivative **56**, which was suitable for addition of Grignard reagent **57**. However, subsequent reduction required some optimization; eventually, **58** was obtained in 64% yield by using a mixture of palladium on charcoal and Raney nickel in methanol as catalyst. Simultaneous removal of the benzyl protection groups in the reduction step was not accomplished. This was achieved with Pearlmans catalyst under 10 bar hydrogen pressure after a reaction time of three days. Hydrolysis of the acetal with hydrochloric acid furnished (+)-prosophylline in a total yield of 55%. The physical and spectral data were in accordance with those reported in the literature {m.p. 82–83 °C; $[\alpha]_D^{20} = +8.4$ ($c = 0.72$, $CHCl_3$); lit.:[2d] m.p. 85.5–86 °C; $[\alpha]_D^{20} = +10.3$ ($c = 1.30$, $CHCl_3$)}.[2d,39]

Conclusion

Enantioselective iridium-catalyzed allylic substitution in combination with ring-closing metathesis constitutes a convenient approach for the preparation of enantiomerically enriched *N*-methoxylactams. From these, *cis*-piperidines or *cis*-pyrrolidines are available through reactions with Grignard reagents or organolithium compounds followed by diastereoselective reductions with Raney nickel or complex metal hydrides/acetic acid. In addition, compounds with a quaternary carbon can be synthesized by reaction with potassium cyanide/AcOH. The procedure was applied in the syntheses of alkaloids (−)-209D and (+)-prosophylline.

Experimental Section

General procedure for alkylation/reduction with H_2/Raney nickel: Under an atmosphere of argon, Grignard reagent (1.2 equiv) was added to a solution of *N*-methoxy-amide (1 equiv) in anhydrous THF (0.2 M). The reaction mixture was stirred at RT for 1–2 h, then water was added, and the resultant mixture was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. A suspension of the crude product and Raney nickel in the stated solvent was stirred under a hydrogen atmosphere (balloon) at RT overnight. The catalyst was removed by filtration through a pad of silica and the filtrate was concentrated in vacuo. The residue was subjected to flash chromatography (petroleum ether/triethylamine, ca. 97:3).

General procedure for alkylation/reduction with complex metal hydrides: Under an atmosphere of argon, Grignard reagent (1.2 equiv) or organolithium reagent (1.2 equiv) was added to a solution of an *N*-methoxy-amide (1 equiv) in anhydrous THF (0.2 M). The reaction mixture was stirred at RT for 1–2 h, then AcOH (1 mL mmol^{-1} of *N*-methoxy-amide) was added dropwise and the mixture was stirred for 10 min before a complex metal hydride (5 equiv) was added. When TLC monitoring indicated complete conversion, aqueous NaOH (10%) was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was subjected to flash chromatography (petroleum ether/ethyl acetate).

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